REVIEW ARTICLE

Essential hypertension and pregnancy

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Approximately 1% of pregnancies are complicated by essential hypertension. During pregnancy the blood pressure often stabilizes or improves. In patients with sustained hypertension, prospective controlled studies have demonstrated enhanced fetal survival when the blood pressure was controlled with antihypertensive medication. Such medication must be chosen carefully to avoid fetal and maternal toxicity, and diuretics and salt restriction during pregnancy should be avoided. Among patients with essential hypertension the problem accelerates late in pregnancy in 2% to 11%; the acceleration may be predicted by determination of maternal mean arterial pressures and intravascular volumes early in pregnancy. The treatment of accelerated hypertension is identical to that of severe pre-eclampsia. Fetal loss is considerable but can be lessened by careful fetal and maternal monitoring and early controlled delivery. The risks of pregnancy in most patients with essential hypertension are small, and essential hypertension is not a uniform contraindication to pregnancy.

Environ 1% des grossesses sont compliquées d'hypertension essentielle. Durant la grossesse la tension artérielle souvent se stabilise ou s'améliore. Chez des patientes souffrant d'hypertension persistante, des études prospectives contrôlées ont démontré une survie foetale améliorée lorsque la tension artérielle a été contrôlée par une médication antihypertensive. Ces médicaments doivent être choisis avec soin afin d'éviter toute toxicité foetale ou maternelle, et les diurétiques ainsi que les régimes hyposodés devraient être évités durant la grossesse. Chez 2% à 11% des patientes souffrant d'hypertension essentielle le problème s'accentue tard durant la grossesse; cette accélération peut être prédite par la détermination, chez la mère, des pressions artérielles et des volumes intravasculaires moyens, tôt durant la grossesse. Le traitement de l'hypertension accélérée est identique à celui d'une pré-éclampsie sévère. La perte foetale est considérable mais elle peut être diminuée par une surveillance foetale et maternelle suivie et un accouchement précoce contrôlé. Pour la plupart des patientes souffrant d'hypertension essentielle les risques de la grossesse sont faibles, et l'hypertension essentielle n'est pas uniformément une contreindication à la grossesse.

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Hypertension, the commonest medical complication of pregnancy, may occur in association with a number of underlying disorders. In most series 70% of hypertensive pregnant women have pre-eclampsia or eclampsia, 25% have essential hypertension and 5% have underlying chronic renal disease.[1,2] Looked at another way, 3% to 4% of all pregnancies are complicated by hypertension due to pre-eclampsia or eclampsia, while 1% are complicated by essential hypertension.[2] Essential hypertension therefore is a not uncommon cause of elevated blood pressure in pregnancy. In this article the diagnosis, clinical course and medical management of this disorder are reviewed.

Hypertension during pregnancy: differential diagnosis

It is difficult to make a diagnosis of essential hypertension in a woman whose elevated blood pressure is being evaluated for the first time during pregnancy. The diagnosis can be made most confidently when the hypertension has been noted prior to pregnancy and its genesis has been determined. In persons first noted to be hypertensive during pregnancy, investigation must be undertaken to separate those with underlying essential hypertension from those with pre-existent chronic renal disease, pre-eclampsia or secondary hypertension. Edema and proteinuria are more common in pregnant women with any of these disorders, and since investigative procedures must be limited during pregnancy accurate diagnosis often must await radiologic and biopsy procedures performed post partum. In such cases it is helpful to obtain prior medical histories and summaries of previous medical assessments. This information, along with the current clinical history and the results of physical examination, microscopic examination and culture of the urine, and determination of serum concentrations of creatinine, electrolytes and uric acid (the last being normal or increased in eclamptic syndromes) and 24-hour urine excretion of protein, often leads to an accurate clinical diagnosis. In addition, 24-hour urine excretion of vanillylmandelic acid, metanephrine and normetanephrine should be measured in women with previously

unevaluated severe hypertension, as pheochromocytoma during pregnancy, though rare, is associated with extremely high maternal and fetal mortality.[3]

Pregnant women with pre-existent renal disease (except for patients with lupus nephritis[4]) are best managed on the basis of the serum creatinine value before pregnancy or at the time of the first consultation during pregnancy.[5] Women with even mild pre-eclampsia should be admitted to hospital for careful monitoring, while those with severe pre-eclampsia (hypertension, edema, proteinuria, oliguria, hyperreflexia and abdominal pain) require hospitalization, sedation, bed rest in the lateral decubitus position, adequate sodium administration, blood pressure monitoring and control, constant and multifaceted fetal monitoring and early delivery.[6] Secondary hypertension during pregnancy is relatively rare and, with the exception of pheochromocytoma and sometimes coarctation of the aorta, is best dealt with definitively post partum.[7] Because it is the purpose of this review to discuss essential hypertension in pregnancy, the management of pregnancy in women with pre-existent renal disease, an eclamptic syndrome or secondary hypertension will not be detailed further.

Essential hypertension

Pathophysiologic considerations and course during pregnancy

In women with essential hypertension the blood pressure may remain stable in early pregnancy or may even fall (generating a false sense of security in the clinician); however, in most such women it will increase sometime during the 2nd or 3rd trimester, and in some instances severe accelerated hypertension will develop. The frequency with which severe accelerated hypertension occurs is controversial; early papers reported a rate as high as 30%,[8] but more recent studies have suggested a rate of 2% to 11%.[9,10] Although better pharmacologic management of hypertension throughout gestation has undoubtedly been one important factor in the reduction of the frequency with which accelerated hypertension develops late in pregnancy, some women whose blood pressure has been maintained at normal levels throughout early pregnancy experience this complication.[11,12]

Patients with essential hypertension in whom accelerated hypertension develops late in pregnancy are universally described as having superimposed pre-eclampsia; however, precise data (for example, from renal biopsy) to support this diagnosis are scanty.[13] Examination of the placenta in such cases reveals decreased placental size and ischemic vascular changes compatible with either hypertension or pre-eclampsia.[14] However, the changes in clotting factors that occur in women with pre-eclampsia have not been demonstrated in pregnant women with essential hypertension.[15] Until more definitive information accumulates, therefore, these patients are best described as having accelerated hypertension, the pathophysiologic features of which remain undetermined.

In general, maternal mortality in essential hypertension is low; however, maternal risk is increased by advanced maternal age, by long-standing hypertension with hypertension-mediated end-organ damage and by the development of accelerated hypertension. Infant birth weights and the incidence of fetal loss do not differ substantially from normal when the blood pressure of women with mild essential hypertension decreases or remains normal throughout pregnancy.[16] However, in women with persistent hypertension during pregnancy, control of the hypertension with antihypertensive agents is of unequivocal value in terms of fetal survival.[12,17] When accelerated hypertension develops the incidence of prematurity and of small infant size for gestational age is high and the fetal mortality is strikingly increased.[1,2,8,16] The development of abruptio placentae may also be more common in women with accelerated hypertension.

Since the cause of accelerated hypertension in women with underlying essential hypertension is not well understood, it is impossible to state with accuracy in which persons it is likely to develop. Page and Christianson[18,19] believe that the mean arterial blood pressure in the 2nd trimester is of predictive value in this regard. In a number of new and interesting studies other investigators have demonstrated that severe hypertension in pregnancy (essential hypertension, essential hypertension with accelerated hypertension, or an eclamptic syndrome) is often accompanied by clinical or laboratory evidence, or both, of decreased intravascular volume.[20] Furthermore, there is evidence that in women with hypertension of any type in whom the blood volume fails to expand normally early in pregnancy the fetal outcome is poor.[21] Bletka and collaborators[22] have demonstrated that normotensive women in whom pre-eclampsia eventually develops have substantial decreases in circulating plasma volume early in pregnancy. These studies suggest that decreased intravascular volume may lead to hormonal and hemodynamic changes designed to increase blood pressure and thereby preserve uteroplacental perfusion. Decreased intravascular volume therefore may be paradoxically associated with striking increases in blood pressure. In the future it may be possible to predict the patients with essential hypertension in whom accelerated hypertension is likely to develop by monitoring factors such as the mean arterial pressure during the 2nd trimester and the degree to which the intravascular volume expands in the early stages of pregnancy.

Management during pregnancy

It is clear that in pregnant women with underlying essential hypertension the outcome of pregnancy will be determined to a certain extent by the degree to which the blood pressure is adequately controlled. Availability of new pharmacologic preparations, advances in biochemical and noninvasive methods of fetal monitoring, and increased understanding of the physiologic aspects of pregnancy have led to significant advances in management.

It has become apparent, for example, that salt restriction has no place in the management of a pregnant woman with essential hypertension, particularly since some investigators have demonstrated that these women have a decreased ability to conserve sodium normally.[23] Sodium restriction may induce a fall in the intravascular volume resulting in a

decrease in renal and uteroplacental perfusion. Through mechanisms detailed above, this may result in a paradoxic increase in blood pressure despite a decrease in intravascular volume.[6,20-22] It has been suggested, in fact, that liberal ingestion of salt may be beneficial in the maintenance of good blood pressure control during pregnancy.[24]

Although no definitive data exist that define the optimum blood pressure to be maintained throughout pregnancy in a woman with essential hypertension, in recent years the indications for initiation of antihypertensive therapy have been better defined. Because too vigorous pharmacologic lowering of the systemic blood pressure may impair uteroplacental perfusion, initiation of antihypertensive therapy in pregnant women is commonly deferred until the diastolic pressure exceeds 100 mm Hg in the 2nd trimester or 110 mm Hg in the 3rd trimester, and it should be the clinician's aim to maintain the diastolic blood pressure at no less than 90 mm Hg.

No antihypertensive medication is uniquely qualified for use in pregnancy. During pregnancy, diuretic-induced volume depletion may interfere with renal and uteroplacental perfusion and, in accordance with the mechanisms outlined above, this may result in a syndrome simulating worsening pre-eclampsia.[25] Thiazide diuretics have also been implicated in fatal maternal hemorrhagic pancreatitis[26] and hyponatremia, and in neonatal thrombocytopenia.[27] More potent diuretics acting on the loop of Henle have an even stronger tendency to produce depletion of the extracellular fluid volume and electrolyte imbalance. Furthermore, furosemide has been reported to cause congenital abnormalities in experiments with animals.[28] During pregnancy, therefore, diuretic agents generally should be avoided, although administration of powerful loop diuretics may be lifesaving in the treatment, for example, of acute left ventricular failure associated with accelerated hypertension.

Alpha-methyldopa is an effective and safe antihypertensive agent in pregnancy.[11,12] With this medication regional blood flow to the kidneys and uterus is relatively well preserved.[29] An initial dose of 125 mg three times daily can be prescribed and the dosage increased as required to a maximum of 500 mg four times daily. Hydralazine, a vasodilating agent, may be used in a daily dose of up to 300 mg. This medication increases cardiac output and renal and uterine blood flow,[29] and is a good antihypertensive agent for use during pregnancy. In nonpregnant persons hydralazine is most effectively combined with the β-blocking agent propranolol. However the latter has recently been linked with cases of multiple fetal abnormalities,[30,31] and it may cause neonatal respiratory depression.[32] The combination of hydralazine and propranolol, therefore, generally should be avoided during pregnancy.

The use of reserpine and guanethidine in pregnancy is limited by the side effects of these agents. There are many well recognized side effects of reserpine therapy that occur in both pregnant and nonpregnant patients; in addition, during pregnancy maternal sensitivity to seizures is increased, and neonatal anorexia, nasal stuffiness and secondary cyanosis and respiratory distress may occur (neonates are obligate nose-breathers). The marked orthostatic hypotension that frequently accompanies guanethidine administration decreases this drug's usefulness in pregnancy. Clonidine and bethanidine have not had wide use in pregnancy, so their safety is largely unknown.

Development of accelerated hypertension

In pregnant women with underlying essential hypertension accelerated hypertension occasionally develops during pregnancy, most commonly in the 2nd or 3rd trimester. The management of such patients is similar to the management of patients with severe pre-eclampsia. They should be hospitalized and rest in bed in the lateral decubitus position. Sedatives may be administered. As it is becoming clear that depletion of the intravascular fluid volume often contributes to the hypertension in these patients, such depletion should be sought, and if found it should be corrected with salt administration.[20,33] Fetal monitoring by standard means is essential. Ultrasonography and amniocentesis with determination of lecithin–sphingomyelin ratios in the amniotic fluid will prove helpful in assessing whether the fetus is mature.[34] Other tests that are important as indexes of the viability of the uteroplacental unit include examination of the amniotic fluid for meconium staining (this may suggest fetal anoxia), serial determination of urinary estriol excretion[35] and of human placental lactogen values,[36] and performance of oxytocin challenge tests[37] and "nonstress tests".[38] (Concomitant administration of antibiotics may artefactually decrease urinary estriol excretion in pregnant women.[39])

Baseline antihypertensive therapy should be continued in these patients, and additional medication should be used to maintain the diastolic blood pressure below 110 mm Hg. When additional medication is required we prefer to use diazepam along with hydralazine administered parenterally.[40] Magnesium sulfate has a long history of success in patients with accelerated hypertension.[6] It has anticonvulsant, hypotensive and sedative properties. A therapeutic blood concentration of 6 to 8 mEq/L should be achieved and there should be frequent clinical monitoring for magnesium intoxication. Pennington and Picker[41] and others have reported success with intravenous administration of diazoxide, a nondiuretic benzothiadiazine. This medication is given rapidly as an intravenous bolus in a dose of 5 mg/kg, and it may be given again in 30 minutes and then every few hours as required. Although effective in controlling accelerated hypertension, this medication causes decreased uterine activity, so that simultaneous administration of oxytocin may be necessary. In addition, diazoxide may result in sodium retention and occasionally fetal and maternal hyperglycemia. Although therapy with clonidine[42] and bethanidine[43] given intravenously has been reported to be successful in the management of pregnant women with accelerated hypertension, experience with these agents is limited; other regimens are probably safer and more effective. Sodium nitroprusside is an important drug in the management of hypertensive crises in nonpregnant persons; however, the possible harmful effects on the fetus of the small amount of cyanide released by the metabolism of this drug prohibits its use during pregnancy. Ganglionic blockers such as pento-

linium tartrate should be avoided, as they cause meconium ileus in the newborn.

If the results of ultrasonography and biochemical study of amniotic fluid suggest that the fetus is mature, delivery should be undertaken as soon as the mother's blood pressure has been stabilized. Alternatively, should the amniotic fluid assessment, urinary estriol values or other parameters of fetal welfare indicate fetal distress, or should the blood pressure be difficult to control, delivery should be undertaken irrespective of fetal maturity. If delivery is indicated and vaginal delivery is not feasible, cesarean section should be performed.

Conclusions

In managing pregnant women with mild to moderate essential hypertension the clinician should try to achieve a stable diastolic blood pressure of 90 to 100 mm Hg. Sodium restriction and diuretic agents generally should be avoided. Antihypertensive therapy is best initiated with α-methyldopa in a dose of up to 2 g/d, and hydralazine without propranolol can be added if required. Should blood pressure control still not be achieved, therapy with agents such as reserpine, guanethidine, clonidine or propranolol can be considered; however, patients requiring these medications should be admitted to hospital for bed rest and careful monitoring. If accelerated hypertension develops, the patient should be admitted to hospital and the blood pressure should be controlled. Using modern methods of maternal and fetal monitoring, the clinician should make a decision regarding early delivery on the basis of fetal maturity and maternal and fetal stability.

Pregnancy in women with underlying essential hypertension is not free of maternal or fetal risk, but the frequency of complications is significantly less today than the rates in frequently quoted early papers. With proper antihypertensive therapy and aggressive maternal and fetal monitoring, the maternal risk should be small and the fetal outlook excellent. Although pregnancy continues to be relatively contraindicated in women with essential hypertension who are older, have cardiovascular or renal disease, or had poorly controlled hypertension prior to pregnancy, in most women essential hypertension should no longer be considered a contraindication to pregnancy.

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